BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Minxue Zheng et al.

Confirmation No. 9085

Application Serial No. 10/667,191

Group Art Unit: 1637

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Examiner: Heather Calamita

Title: DUAL-PURPOSE PRIMERS AND PROBES FOR PROVIDING ENHANCED HYBRIDIZATION ASSAYS BY DISRUPTION OF SECONDARY STRUCTURE FORMATION

REPLY BRIEF

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Commissioner for Patents
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Sir:

Responsive to the Examiner's Answer, mailed from the USPTO on October 6, 2008, applicants respectfully request the Board's consideration of the arguments set forth in this paper. This Reply Brief is timely filed within two months of the mailing date of the Examiner's Answer. The arguments set forth in this paper provide replies to the Examiner's "Response to Arguments" set forth at Item 10, pages 17-25, of the Examiner's Answer (also referred to herein as "the paper under reply").

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I. STATUS OF THE CLAIMS

Claims 1-39 are pending in the instant application. Of the pending claims, claims 1-18 and 26-35 were rejected in the non-final Office Action of December 28, 2007, and are under appeal. Claims 19-25 and 36-39 have been withdrawn from consideration as drawn to a non-elected invention. Following is a listing of all of the pending claims with status identifiers:

1. **(Previously presented)** A dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

2. **(Original)** The primer of claim 1, wherein the site of interest is a nucleic acid sequence.

3. **(Original)** The primer of claim 2, wherein the site of interest is a single nucleotide polymorphism.

4. **(Original)** The primer of claim 1, wherein the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence.

5. **(Original)** The primer of claim 1, further including a nonhybridizing spacer between the primer sequence and the blocking sequence.

6. **(Original)** The primer of claim 5, wherein the spacer is non-nucleotidic.

7. **(Original)** The primer of claim 6, wherein the spacer is comprised of a synthetic hydrophilic oligomer.

8. **(Original)** The primer of claim 7, wherein the spacer is comprised of about 3 to about 50 alkylene oxide units selected from ethylene oxide and combinations of ethylene oxide and propylene oxide.

9. **(Original)** The primer of claim 5, wherein the spacer is nucleotidic.

10. **(Original)** The primer of claim 9, wherein the spacer is comprised of a sequence of non-natural nucleotides.

11. **(Original)** The primer of claim 10, wherein the non-natural nucleotides are selected from iso-guanine and iso-cytosine.

12. **(Previously presented)** The primer of claim 9, wherein the spacer is an oligomeric segment of a recurring single nucleotide.

13. **(Original)** The primer of claim 9, wherein the probe sequence and the spacer are separated from each other by a means for halting transcription therebetween.

14. **(Original)** The primer of claim 13, wherein the means for halting transcription is an arresting linker.

15. **(Original)** The primer of claim 14, wherein the arresting linker comprises at least one modified nucleoside.

16. **(Original)** The primer of claim 15, wherein the modified nucleoside is an N^4-modified pyrimidine.

17. **(Original)** The primer of claim 1, further comprising a detectable label.

18. **(Original)** The primer of claim 17, wherein the detectable label is selected from the group consisting of fluorescers, chemiluminescers, dyes, biotin, haptens, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, enzyme subunits, metal ions, electron-dense reagents, and radioactive isotopes.

19. **(Withdrawn)** A method for amplifying a target nucleotide sequence in a target molecule, wherein the target nucleotide sequence contains a site of interest proximal to or contained within a secondary structure forming region capable of forming an unwanted secondary structure in an amplicon formed under amplification conditions, comprising: contacting the target nucleotide sequence under hybridizing conditions, together or sequentially, with a dual-purpose primer according to claim 1 complementary to one terminus of a first strand of the target molecule, a second primer complementary to the opposing terminus of the second strand of the target molecule, nucleotides appropriate to said amplification, and an agent for polymerization of the nucleotides, wherein amplicons formed during said method do not contain the unwanted secondary structure, such that the site of interest is accessible to a hybridizing oligonucleotide.

20. **(Withdrawn)** The method of claim 19, wherein the agent for polymerization is a DNA polymerase.

21. **(Withdrawn)** The method of claim 19, wherein the agent for polymerization is a DNA ligase.

22. **(Withdrawn)** The method of claim 19, wherein the agent for polymerization is an RNA polymerase.

23. **(Withdrawn)** The method of claim 19, wherein the agent for polymerization is an RNA reverse transcriptase.

24. **(Withdrawn)** In a method for conducting the polymerase chain reaction (PCR) to amplify a sequence of a double-stranded target DNA molecule having a first terminus and a second terminus, which comprises (a) heating a sample containing the double-stranded DNA to a temperature effective to denature the DNA and thereby provide a first single strand of DNA and a second strand of DNA, (b) contacting the denatured DNA with first and second oligonucleotide primers each comprised of a target binding sequence complementary to the first terminus of the first DNA strand and to the second terminus of the second DNA strand, respectively, (c) cooling the sample so as to allow hybridization of first and second oligonucleotide primers to the first and second strands of DNA, respectively, (d) replicating the DNA using a DNA polymerase, and repeating the aforementioned steps (a) through (d) to provide multiple copies of the sequence of double-stranded DNA, the improvement comprising employing as the first primer a dual-purpose primer according to claim 1.

25. **(Withdrawn)** The primer of claim 24, wherein the detectable label is selected from the group consisting of fluorescers, chemiluminescers, dyes, biotin, haptens, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, enzyme subunits, metal ions, electron-dense reagents, and radioactive isotopes.

26. **(Original)** An amplicon formed by the action of a DNA polymerase on the primer of claim 1 hybridized to the target nucleotide sequence.

27. **(Original)** A kit for determining the genotype of an individual, comprising a dual-purpose primer according to claim 1, nucleotides appropriate to amplification of an oligonucleotide sequence, and an agent for polymerization of the nucleotides.

28. **(Original)** A kit for determining the genotype of an individual, comprising a dual-purpose primer according to claim 1, a second primer, nucleotides appropriate to DNA amplification, an agent for polymerization of the nucleotides, an allele specific hybridization (ASH) probe having a nucleotide capture region, and color-coded detecting means having a nucleotide capture region complementary to the nucleotide capture region on said ASH probe, wherein the nucleotide capture region on said detecting means is complementary to said ASH

probe such that the target nucleotide sequence is identified by the color-coding of said detecting means.

29. **(Original)** The kit of claim 28, wherein the detecting means is a multiplex detecting means.

30. **(Original)** The kit of claim 29, wherein the multiplex detecting means comprises a detectable solid substrate.

31. **(Original)** The kit of claim 30, wherein the detectable solid substrate is a detectable microsphere.

32. **(Previously presented)** A hybridization probe comprising (a) a probe nucleotide sequence complementary to a first nucleotide sequence in a target molecule, and (b) a blocking sequence substantially complementary to a second nucleotide sequence located within a secondary structure formation in the target molecule, wherein the secondary structure formation interferes with hybridization of the probe nucleotide sequence to the first nucleotide sequence and further wherein hybridization of the blocking sequence with the second nucleotide sequence disrupts the secondary structure formation in the second nucleotide sequence such that the probe nucleotide sequence is able to hybridize to the first nucleotide sequence.

33. **(Original)** The hybridization probe of claim 32, further comprising a detectable label.

34. **(Original)** The hybridization probe of claim 33, wherein the detectable label is selected from the group consisting of chemiluminescent labels, fluorescent labels, radioactive labels, multimeric DNA labels, dyes, enzymes, enzyme modulators, detectable solid substrates, and metal ions.

35. **(Previously presented)** A method of performing a hybridization assay for detecting the presence of a target nucleotide sequence in a target molecule, wherein the target nucleotide sequence is proximal to or contained within a secondary structure forming region capable of

forming an unwanted secondary structure that would prevent detection of the target nucleotide sequence, the method comprising: contacting the target molecule under hybridizing conditions with the hybridization probe of claim 33, such that hybridization of the probe to the target molecule disrupts formation of the unwanted secondary structure and allows detection of the target nucleotide sequence.

36. **(Withdrawn)** The method of claim 35, wherein the target molecule is obtained from a human individual.

37. **(Withdrawn)** The method of claim 35, wherein the target molecule is bacterial in origin.

38. **(Withdrawn)** The method of claim 35, wherein the target molecule is viral in origin.

39. **(Withdrawn)** The method of claim 38, wherein hybridization of the first hybridization probe sequence with the target nucleotide sequence is diagnostic of a disease caused by the virus.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether the Examiner's claim interpretation is proper.
2. Whether claims 1-18 and 26-35 lack an adequate written description under 35 U.S.C. § 112, first paragraph.
3. Whether claims 1-18 and 26-35 are anticipated under 35 U.S.C. § 102(b) by Wilton et al., *Human Mutation* (1998) (hereinafter "Wilton et al.").
4. Whether claims 1, 2 and 4-7 are anticipated under 35 U.S.C. § 102(b) by USPN 5,573,906 to Bannwarth et al. (hereinafter "Bannwarth et al.").
5. Whether claims 1 and 5-8 are anticipated under 35 U.S.C. § 102(b) by U.S. Publication No. 2002/0028455 to Laibinis et al. (hereinafter "Laibinis et al.").
6. Whether claims 1, 17, and 18 are anticipated under 35 U.S.C. § 102(b) by USPN 6,268,147 to Beattie et al. (hereinafter "Beattie et al.").
7. Whether claims 27-32 are rendered obvious under 35 U.S.C. § 103(a) over Wilton et al. in view of Stratagene's 1998 Catalog (hereinafter "Stratagene").
8. Whether claim 28 is rendered obvious under 35 U.S.C. § 103(a) over Bannwarth et al. in view of Stratagene.
9. Whether claims 28-34 are rendered obvious under 35 U.S.C. § 103(a) over Beattie et al. in view of Stratagene.
10. Whether claims 10, 11, 15, and 16 are rendered obvious under 35 U.S.C. § 103(a) over Wilton et al. in view of USPN 6,054,568 to Fisher (hereinafter "Fisher").

III. ARGUMENT

A. THE EXAMINER'S CLAIM INTERPRETATION IS NOT PROPER

With this paper, applicants maintain that the Examiner's rejections are premised on faulty claim interpretation.

Claim 1 reads as follows:

> A dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest.

As indicated on pages 19-24 of the Examiner's Answer, the Examiner is not giving patentable weight to the sections of the claim that are highlighted in italics and bold italics below on the grounds that the italicized portions of claim 1 are intended use language and that bold italicized portions of claim 1 are functional language directed to the target.

> A dual-purpose primer *for amplifying a target nucleotide sequence in a target molecule*, ***wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region*** wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than ***the secondary structure forming region***; and (b) a blocking sequence substantially complementary ***to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest***.

When the recitations of claim 1 that the Examiner alleges have no patentable weight are removed, claim 1 is reduced to the following:

> A dual-purpose primer, wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence and (b) a blocking sequence.

Such destruction of the scope of applicants' claim is improper, inaccurate, and in contravention of well-established Federal Circuit precedent. The following discussion will address the errors in the Examiner's analysis and will also provide the Board with reasons for remanding this case to the Examining Corps for allowance.

First, applicants take issue with the Examiner's position that the italicized language in the preamble is intended use language that is to be accorded no patentable weight. The law with respect to preamble language is well-developed and proper application of the law will readily demonstrate that the italicized language is language that must be given patentable weight.

In *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997), the Federal Circuit explained the difference between preamble language that is to be afforded patentable weight and intended use language that is not with the following statement:

> In general, a preamble limits the invention if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim…Conversely, a preamble is not limiting where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.

The following discussion will outline the law on limiting preamble claim language and will explain why the italicized language from claim 1 is not intended use language.

In the 2002 case *Catalina Marketing International, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801 (Fed. Cir. 2002), the Federal Circuit explained that although there is no litmus test that defines when a preamble limits claim scope, guideposts have emerged from various cases that define a preamble's effect on claim scope. Such defining guideposts include (i) claims that rely on preamble claim terms for antecedent basis and (ii) reliance by applicants on preamble claim terms to define the invention over the prior art.

With respect to (i), the Federal Circuit has held that if claim terms in the body of the claim rely on specific terms in the preamble for antecedent basis, then the specific terms in the preamble serve to define the claimed invention. *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995) ("[W]hen the claim drafter chooses to use *both* the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects."). Likewise, when the preamble is essential to understand limitations or terms in the claim body, the preamble limits claim scope. *Pitney Bowes, Inc. v. Hewlett Packard Co.*, 182 F.3d 1298, 1306 (Fed. Cir. 1999).

In the instant case, removal of the language italicized by the Examiner from the claim results in a claim that lacks antecedent basis for the claim terms "target molecule" and "target nucleotide sequence" as shown below:

> A dual-purpose primer, ***wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region*** wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than ***the secondary structure forming region***; and (b) a blocking sequence substantially complementary ***to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest***.

In view of the foregoing, it follows that the preamble term " a target nucleotide sequence in a target molecule" is necessary language in order to provide antecedent basis for the terms "the target nucleotide sequence" and "the target molecule" in the body of claim 1.

With respect to (ii), the Federal Circuit has held that clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention. *Bristol Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001).

In the prior responses to the rejections over Beattie et al., applicants explained that among other distinguishing factors, the probes of Beattie et al. are intended only to identify the sequence of a target analyte and are not intended to amplify the target strand. *See*, Response dated Nov. 8, 2006, p. 9; Response dated July 27, 2007, p. 15; Appeal Brief dated July 9, 2008, p. 20. In view of the foregoing, it follows that the preamble term "amplifying" is used as a claim limitation to define the scope of the dual-purpose probe as a probe that amplifies a target nucleotide sequence in a target molecule. Indeed, amplification is in fact one of the "dual purposes" of the claimed primer, the other being the ability of the probe to disrupt secondary structure formation in a resulting amplicon.

The foregoing discussion demonstrates that the italicized language from claim 1 is not intended use language that is to be given no patentable weight; rather, the italicized language represents language that applicants have used to assist in defining the invention and which give

life, meaning, and vitality to the claim by providing antecedent basis for terms in the body of the claim and also by providing claim terms that are integral to the proper interpretation of the remainder of the claim.

Second, the Examiner's assertion that the bold italicized language is not to be accorded any patentable weight because it is functional language directed to the target and not the primer is not accurate and should not be followed.

Solely for purposes of argument, in the discussion that follows, applicants will address the Examiner's arguments under the rubric that the bold italicized language is functional language; however, applicants are not agreeing with the Examiner's position that the language is functional and maintain that the language is structural for the reasons set forth in the Appeal Brief. Nevertheless, the following discussion is necessary for rebuttal purposes in order to show that regardless of whether the language of claim 1 is considered functional or structural, the outcome is the same; specifically, that the bold italicized language of claim 1 is limiting language that must be accorded patentable weight.

With respect to the patentability of functional claim language, applicants direct the Board's attention to MPEP § 2173.05(g), which provides a significant amount of guidance on this issue. Citing *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971), the MPEP explains that there is nothing inherently wrong with defining some part of an invention in functional terms and that functional language does not, in and of itself, render a claim improper. MPEP § 2173.05(g), p. 2100-226 (Rev. 7, July 2008). The MPEP further provides that a functional limitation *must* be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step. The MPEP cites two cases that illustrate limiting functional language.

In *In re Barr*, 444 F.2d 588, 170 USPQ 33 (CCPA 1971), it was held that a limitation used to define a radical on a chemical compound as "incapable of forming a dye with said oxidizing developing agent," although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought. In *In re Venezia*, 530 F.2d 956, 189 USPQ 149 (CCPA 1976), the claim at issue was directed to a kit of component parts capable of being assembled; the Court held that limitations such as "members adapted to be positioned" and "portions . . . being resiliently

dilatable whereby said housing may be slideably positioned" served to precisely define structural attributes of interrelated component parts of the claimed assembly.

As explained in paragraph 0007 of the instant application, the claimed dual purpose primer is designed to overcome the need in the art for an improved hybridization probe that detects sequences contained within regions of a target molecule that tend to form unwanted secondary structure. The claimed primer overcomes this need in the art by providing the claimed dual purpose primer, a primer whose purpose is (i) to amplify a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and the target nucleotide sequence contains a site of interest proximal to or contained within the secondary structure forming region, and (ii) to disrupt secondary structure formation in the resulting amplicon thereby enabling amplification of the site of interest.

Because the dual purpose primer is intended to amplify target sequences contained within a secondary structure region of a target molecule, the claim must include recitations directed to the target molecule in order to accurately define the primer. To be sure, removing references to the target molecule, as the Examiner did to claim 1 in the paper under reply, reduces claim 1 to a recitation of a primer that applicants are not asserting as their invention. As already noted, removal of the references to the target molecule results in a claim with the following language:

> A dual-purpose primer, wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence and (b) a blocking sequence.

The Examiner's failure to consider more than three-quarters of the claim renders claim 1 to little more than a recitation of a primer being complementary to a target sequence. Further, the recitation of the claim term "blocking sequence" has no meaning when the context of the secondary structure formation within the target molecule is removed.

The limitations of the claimed invention are similar to those discussed in the two cases cited in Section 2173.05(g) of the MPEP: *In re Barr* and *In re Venezia*.

The broadest claim in *In re Barr* had the following language:

> 23. A photographic color coupler capable of forming a dye and a mercaptan when reacted with oxidized aromatic primary amino color developing agent and having the formula COUP-S-R wherein
>
> COUP is a photographic color coupler radical selected from the group consisting of a 5-pyrazolone coupler radical and an open-chain ketomethylene coupler radical,

> COUP having substituted in its coupling position the monothio radical; and
>
> R is an organic radical incapable of forming a dye with said oxidized developing agent and being selected from the group consisting of an alkyl radical, a cycloalkane radical, an aryl radical and a heterocyclic radical containing at least one hetero atom selected from the group consisting of oxygen, sulphur and nitrogen.

Claim 23 is a composition claim directed a photographic color coupler. The functional language at issue concerned the limitation relating to R being incapable of forming a dye with the oxidized developing agent recited in the claim. The Court of Customs and Patent Appeals (CCPA) held that the functional language was limiting because it defined a known class of radicals and set a definite boundary on the patent protection sought. *In re Barr*, 444 F.2d at 594-598. Like the radicals in *In re Barr*, the target molecule of the claimed invention is limiting because it defines a specific class of target molecules, i.e., those having unwanted secondary structure formation, and consequently sets a definite boundary on the patent protection sought.

A representative claim at issue in *In re Venezia* had the following language (relevant language that was at issue is highlighted in italics):

> 31. A splice connector kit having component parts capable of being assembled in the field at the terminus of high voltage shielded electrical cables for providing a splice connection between first and second such cables, said cables each having a conductor surrounded by an insulating jacket within a conductive shield wherein a portion of the conductive shield is removed to expose the insulating jacket and a portion of the insulating jacket is removed to expose the conductor at the terminus of the cable, the kit comprising the combination of:
>
> *a pair of sleeves* of elastomeric material, *each sleeve of said pair adapted to be fitted over the insulating jacket of one of said cables*, each said sleeve having an external surface and a resiliently dilatable internal bore for gripping the insulating jacket to increase the dielectric strength of the creep path along the insulating jacket;
>
> *electrical contact means* adapted to be affixed to the terminus of each exposed conductor for joining the conductors and making an electrical connection therebetween;
>
> *a pair of retaining members* adapted to be positioned respectively between each of said sleeves fitted over the insulating jacket of

> each said cable and the corresponding terminus of each said cable, said retaining members each having means cooperatively associated therewith for maintaining each said member's position relative to the insulating jacket on each said cable and for precluding axial movement of the sleeve toward the corresponding terminus of each said cable; and
>
> *a housing*, said housing having an internal bore extending therethrough from end to end, said housing including portions adjacent each end thereof defining said internal bore and being resiliently dilatable whereby *said housing may be slideably positioned* over one of said cables and then slideably repositioned over said sleeves, said retaining members, and said contact means *when said sleeves, said retaining members and said contact means are assembled on said cables* as hereinaforesaid, said resiliently dilatable portions of said housing respectively gripping the corresponding external surface of each said sleeve in watertight sealing relationship therewith and said housing having a further portion intermediate its ends defining said internal bore and forming a sealed chamber enclosing at least said contact means and the exposed portions of said cable conductors when said housing is in its repositioned location.

Claim 31 is directed to a splice connector kit having the following component parts capable of being assembled: a pair of sleeves; electrical contact means; a pair of retaining members; and a housing. The kit was meant to be assembled at the terminus of high voltage shielded electrical cables for providing a splice connection between the first and second cables. The functional language at issue in the case concerned the sleeves being adapted to fit over the insulating jacket of one of the cables; the housing being slideably positioned over the cables; and the sleeves, the retaining members, and the electrical contact means being assembled on the cables. The CCPA held that the functional language was limiting because rather than being a mere direction of activities to take place in the future, the language imparted a structural limitation to the sleeve. *In re Venezia*, 530 F.2d at 959. Like the cable in *In re Venezia*, which engaged with the housing, sleeves, retaining members, and electrical contact means, the target molecule of the claimed invention imparts structural limitations to the primer because it engages with the primer.

B. THE EXAMINER'S WRITTEN DESCRIPTION ANALYSIS IS NOT PROPER

The Examiner's assertion that the claimed invention requires a sequence is a direct result of the Examiner failing to give any weight to the recitation relating to the target molecule and thus

reducing the claim to little more than a recitation of a primer and its complement. Indeed, under the Examiner's claim interpretation, arguably a sequence would be necessary in order to provide some degree of definition to the primer; however, when the bold italicized language relating to the target molecule is afforded its proper patentable weight, there is no reason to define the primer with a sequence because the bold italicized language serves to define the structural limitations of the primer and provides the metes and bounds of the claimed invention.

C. THE EXAMINER'S INHERENT ANTICIPATION ANALYSIS IS NOT PROPER

At pages 20-25 of the paper under reply, the Examiner attempts to justify the rejection of the claimed invention over Wilton et al., Bannwarth et al., Laibinis et al., and Beattie et al. by taking the position that the references inherently anticipate the claimed invention. Applicants submit that the Examiner's inherent anticipation arguments are not proper and must not be followed.

The law on what constitutes a *prima facie* case of anticipation is well-established; it provides that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 at 2100-67, citing, *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The Federal Circuit has held that "[a]fter the PTO establishes a *prima facie* case of anticipation based on inherency, the burden shifts to the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied upon." *In re King*, 801 F.2d 1324 (Fed. Cir. 1986).

The Examiner's failure to properly consider each and every element of the claimed invention is discussed in detail above. When each of the limitations of the claimed invention are properly considered, it is readily apparent that the cited references do not anticipate the claimed invention, either expressly or inherently, for the reasons set forth in the Appeal Brief. Notwithstanding the foregoing, a discussion of the flaws in the Examiner's inherent anticipation analysis is necessary in order for the Board to fully appreciate the Examiner's failure to establish a *prima facie* case of anticipation of the claimed invention.

In each of the art-based discussions set forth at pages 19-25 of the paper under reply, the Examiner expressly states that the target is not present in any of the cited references. *See*, Examiner's Answer, p. 20, 1st para.; p. 21, 2nd full para.; p. 23, 1st full para.; p. 24, 1st full para.

("Appellants are claiming only the primer, therefore the target does not need to be present in the prior art document."). To justify the missing teaching, the Examiner uses the rationale that each of the cited references "inherently meet the functional limitations of clause (b) (i.e., the blocking sequence clause of claim 1) when an appropriate target is present." Applicants submit that this rationale is inappropriate and incorrect.

MPEP § 2131.01 explains that when a reference is silent about an inherent characteristic, such gap in the reference should be filled with recourse to extrinsic evidence that clearly shows that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill in the art. MPEP § 2131.01 at 2100-68, citing, *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

The Examiner's arguments at pages 19-25 of the paper under reply do not reference extrinsic evidence to supplement the missing teachings; rather, what the arguments do is pull random sequences from the cited references, use them to formulate hypothetical target molecules that are not taught or suggested in the references, and use the made-up target molecules to assert that the random sequences inherently read on the claimed primers. Applicants submit that this approach by the Examiner does not constitute an examination of the claimed invention; it is a fabrication designed solely to justify the improper rejection of the claimed invention. The Federal Circuit has condemned such an approach by explaining that "a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination." *In re Newell*, 891 F.2d 899, 901 (Fed. Cir. 1989), *cert. denied*, 493 U.S. 814 (1989). In other words, as further elaborated by the Federal "Circuit, "[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency." *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993), *citing*, *In re Oelrich,* 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981) (emphasis added by the *Rijckaert* Court).

As discussed in detail in the Appeal Brief, the cited references do not teach or suggest the claimed invention. Wilton et al. teach snapback primers that are designed to form secondary structures that allows for the identification of target nucleotides through altered migration of the target through a polyacrylamide gel. Bannwarth et al. also teach a primer that is meant to fold back upon itself and form a secondary structure for facilitating detection of a target molecule. Laibinis et al. teach a method of linking a target moiety, which may or may not have secondary or

tertiary structure, to support-bound oligonucleotides. Beattie et al. teach the tandem hybridization of labeled oligonucleotides to avoid spontaneous formation of secondary structures in single stranded target nucleotides.

In the paper under reply, the Examiner asserts that the A(f) snapback primer of Table 1 of Wilton can disrupt secondary structure formation of the hypothetical target set forth on page 20 of the paper under reply. Applicants are not convinced that the primer of Wilton et al. can in fact disrupt the secondary structure formation of the hypothetical target. The figure at page 20 of the Office Action appears to show that the underlined sequence will bind to its complementary sequence on the target, but applicants do not see how the italicized segment of the primer will bind to its complement on the hypothetical target. Indeed, the italicized segment of the target appears to already be fully bound to its complement in a hairpin loop. In view of the foregoing, it would appear that the Examiner's figure would require some additional step in order to separate the bound sequence in the hairpin loop so that one strand of the hairpin target sequence may bind to the italicized section of the primer sequence. Applicants are applying this same traversal argument to the Examiner's discussion regarding primer 15 of Bannwarth et al. (Examiner's Answer, p. 22); the PCR primers of Beattie et al. (Examiner's Answer, p. 23); and SEQ ID NO. 2 of Beattie et al. (Examiner's Answer, p. 24).

Turning to the issue of the basis for the figures set forth at pages 20, 22, and 24 of the paper under reply, pursuant to MPEP §§ 2144.02 and 2144.03, applicants are objecting to the presentation of these figures and all arguments relating to the figures as not supported by the record or the cited art. On this matter, if the figures and the accompanying arguments are based upon the Examiner's judicial notice of scientific evidence and/or facts that are not of record, then pursuant to MPEP § 2144.03, the Examiner should have provided applicants with documentation of the additional facts and/or scientific evidence so that applicants could review the facts/evidence and have the opportunity to respond to same. In particular, applicants would have liked to know how the target sequences set forth in the figures on pages 20, 22, and 24 were derived. If the Examiner fabricated the target sequences based solely on personal knowledge then pursuant to MPEP § 2144.03(C) and 37 C.F.R. § 1.104(d)(2), the Examiner should have provided applicants with an affidavit or declaration setting forth specific factual statements and explanations to support the personal knowledge.

Because the Examiner's Answer is the first time that the Examiner has raised the argument that the anticipation rejections are based upon inherency and it is also the first time that applicants have had the opportunity to see the how the Examiner believes that the sequences from the cited references would react to hypothetical target molecules that are outside of any teachings of the cited references, applicants respectfully request that the Board disregard the Examiner's inherent anticipation arguments as incomplete, insufficient, and untimely.

D. THE OBVIOUSNESS REJECTIONS

Applicants have no additional comments to add to the obvious rejections over those set forth in the Appeal Brief.

E. THE CLAIM TERM "SUBSTANTIALLY COMPLEMENTARY"

Applicants acknowledge with appreciation the Examiners confirmation that the claim term "substantially complementary" is proper.

F. CONCLUSION

In closing, applicants respectfully request that the Board consider all of the claim limitations set forth in the pending claims. When all of the limitations of the claim are properly considered, it will become readily evident that the claimed invention is supported by the written description and that the claimed invention is novel and non-obvious over the cited art for the reasons set forth in the Appeal Brief.

Respectfully submitted,

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